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EXAMINER	
JAISLE, CECILIA M	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/595,734	MARTIN ET AL.	
	Examiner	Art Unit	
	CECILIA M. JAISLE	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☒ Claim(s) *31-36* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05-08-2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Lack of Unity

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

I. Claims 1-36, drawn to compositions and methods comprising a compound of Formula (I) in which R2 is aryl, cycloalkyl, aralkyl, -OR8, -S(O)tR6, -N(R7)R8, -N(R9)S(O)tR10, -C(O)R6 , -C(O)OR6, or -C(O)N(R7)R8, or of Formula (II), classified in class 514, subclasses 247, 269, *inter alia*.

II. Claims 1 and 11-36, drawn to compositions and methods comprising a compound of Formula (I) in which R2 is heteroaryl, heterocyclyl, or heteroaralkyl, classified in class 514, subclasses 247, 269, *inter alia*.

III. Claims 1 and 11-36, drawn to compositions and methods comprising a compound of Formula (I) in which R2 and R3, together with the carbon atom to which they are attached, form a thieno-fused ring, classified in class 514, subclass 260.1, inter alia.

IV. Claims 1 and 11-36, drawn to compositions and methods comprising a compound of Formula (I) in which R2 and R3, together with the carbon atom to

which they are attached, form a benzopyrano-fused ring system, classified in class 514, subclass 267, inter alia.

V. Claims 1 and 11-36, drawn to compositions and methods comprising a compound of Formula (I) in which R2 and R3 are other than as provided for by Groups I-IV, classified in class 514, subclasses 247, 260.1, 267, 269, inter alia.

If Group V is elected, further election may be required. Each group as set forth above lacks unity with each other group, i.e., there is no single general inventive concept. The unique special technical features in each group are the identities of the compounds in regard to the R2 and R3 substituents. The technical relationship between the inventions does not involve at least one common or corresponding special technical feature. The expression "special technical feature" is defined as meaning those technical features that define the contribution which each claimed invention, considered as a whole, makes over the prior art. In this case, a reference that could be used to reject the compositions and methods of Group I could not be used to reject the compositions and methods of Groups II-V.

The Group I invention has special technical features not common to Groups II-V and would be expected to be useful other than as disclosed, e.g., as herbicides (US 5849758; cited by Applicants).

Restriction for examination purposes as indicated is proper because the inventions listed in this action are lacking in unity and are independent or distinct for the reasons given above and there would be a serious search and examination burden if restriction were not required because one or more of the following reasons apply:

(a) the inventions have acquired a separate status in the art in view of their different classification;

(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;

(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);

(d) the prior art applicable to one invention would not likely be applicable to another invention;

(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

During a telephone conversation with Mr. Michael Greenfield on April 17, 2008 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-36, drawn to compositions and methods comprising a compound of Formula (I) in which R2 is aryl, cycloalkyl, aralkyl, -OR8, -S(O)tR6, -N(R7)R8, -N(R9)S(O)tR10, -C(O)R6 , -C(O)OR6, or -C(O)N(R7)R8, and of Formula (II). Applicant must affirm this election in replying to this Office action. Claims 1-36 are under examination only to the extent that they are drawn to the elected subject matter as described above. Otherwise, claims 1-36 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is advised that a complete reply to this requirement must include (i) election of an invention to be examined though the requirement is traversed (37 CFR 1.143) **and (ii) identification of claims encompassing the elected invention.**

The election of an invention may be made with or without traverse. To reserve a right to petition, election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the lack of unity requirement, election shall be treated as an election without traverse. Traversal must be presented at the time of election to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

If applicants traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions are obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Rejections Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for binding of the claimed compounds to the RXR protein and the NGFI-B/RXR heterodimer protein complex, does not provide reasonable enablement for a method of altering the activity of a NGFI-B family member (claims 15, 16), a method for the treatment, prevention or amelioration of symptoms of a disease or disorder modulated by NGFI-B family (claims 17, 18), where the disease or disorder is selected from Parkinson's disease (PD), cancer, Alzheimer's disease (AD), schizophrenia, manic depressive illness (bipolar disorder), multiple sclerosis (MS), neuronal inflammatory responses, neuronal injury, stroke, neuronal degeneration, inflammation, acute inflammatory reactions, osteoporosis, arthritis, rheumatoid arthritis (MA), psoriatic arthritis, sarcoid arthritis, osteoarthritis, ulcerative colitis, thyrroiditis, atherosclerosis, and atherosclerosis related cardiovascular and coronary heart disease (claims 19, 24-30), a method of regulating activity of NGFI-B by incubating a stem cell with a claimed compound (claims 20-22), a method of maintaining neuronal cell viability after transplantation by administering to a donor recipient [??] a claimed compound (claim 23). The following reasons apply.

Many if not most diseases said to be prevented or controlled by the claimed compounds, cancer, AD, PD, etc., are known as difficult to treat. Although the present specification asserts that all of the claimed compounds alter the activity of a NGFI-B family member, only binding of the claimed compounds to the RXR protein and the NGFI-B/RXR heterodimer protein complex activity is demonstrated. Substantiation of the method of use is required when utility is "speculative," "sufficiently unusual" or not provided. See *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). Also, note *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding types of testing needed to support *in vivo* uses.

Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099 (2001), emphasizing that "a claimed invention must have a specific and substantial utility." See also MPEP 2163, *et. seq*. The disclosure in this application is not sufficient to enable the instant method claims based solely on anti-hypolipaemic activity. The state of the art, as exemplified by the references discussed supra, is indicative of the requirement for undue experimentation. Thus, ability of a compound that modulates kinase activity to prevent or ameliorate all of the diseases/conditions recited by the present claims remains open to proof.

Many factors require consideration when determining whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) the claim breadth; (2) the nature of the invention; (3) the state of the prior art; (4) the level of predictability in the art; (5) the amount of direction provided by the

inventor; (6) the presence of working examples; and (7) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013 (Fed.Cir. 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement:

1. **Breadth of the claims:**

(a) Scope of the methods. The claims cover pharmaceutical methods using millions of substituted pyrimidine compounds. The claims cover treatment of all recited diseases (claims 19, 24-30) and all disorders/diseases related to NGFI-B (claims 15-18 and 20-23). See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as pharmaceutical arts.

The scope of treatment of cancer, for example, is not enabled based on procedures the specification provides.

(b) Scope of the diseases covered. The diseases construed by the claims are as described above.

Regarding the claims that recite "prevention" (claims 17-19 and 24-30), the disclosure does not teach how to identify a host with the potential to develop such disorders or how to provide preventive measures to the identified host. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as pharmaceutical arts. In addition, "prevention" includes prevention of all

sequelae conditions caused by or associated with such disorders that are known to exist and that may be discovered in the future, for which no enablement is provided.

The scope of prevention is not enabled based on procedures the specification provides. "Prevent" means *to keep from happening, preclude, anticipate,* etc. (Webster's Comprehensive Dictionary, 1996). The specification fails to teach one skilled in the art how to identify the host and therapeutic regimen for administration of the instant compounds to achieve the desired preventive effect. No evidence of record enables a skilled artisan to identify hosts with the potential to develop the disorders described herein.

Regarding claims to treatment of cancer, this includes breast and colon cancers, carcinomas of the prostate, lymphoma, leukemia and many others. Breast cancers come in great variety. The most important category of breast cancers is the ductal cancers, which come in a wide variety of types, divided into categories: intraductal (*in situ*); invasive with predominant intraductal component; invasive, NOS; comedo; inflammatory (IBC); medullary with lymphocytic infiltrate; mucinous (colloid) carcinoma; papillary carcinoma; scirrhous; tubular and others. Another category is lobular breast cancers: *in situ*, invasive with predominant *in situ* component and invasive. Paget's disease of the nipple can be also with intraductal carcinoma or with invasive ductal carcinoma. Adenomyoepithelioma is a dimorphic tumor characterized by the presence of both epithelial and myoepithelial cells. There is breast angiolipoma and spindle cell lipoma of the breast. There is lymphoma of the breast (which exists in both Non-Hodgkin's lymphoma of the breast and Hodgkin's disease

of breast forms). There are some sarcomas, including giant cell sarcoma of the breast, leiomyosarcoma of the breast, Angiosarcoma of the breast, cystosarcoma phylloides and liposarcoma of the breast. There are carcinoid tumors that can be primary carcinoid tumors of the breast or can arise from nonmammary sources. There are breast salivary gland-like tumors, including acinic cell carcinoma (AcCC), oncocytic carcinoma (Mammary epithelial oncocytoma) and mucoepidermoid carcinoma (MEC). Other rare carcinomas include Spindle cell carcinoma of the breast (SpCC), Squamous cell carcinoma of the breast, Secretory Carcinoma of the Breast (Juvenile secretory carcinoma), Metaplastic carcinoma of the breast (a heterogeneous group of invasive breast cancers including types with squamous differentiation and those with heterologous elements), Invasive Micropapillary Carcinoma of the Breast, Adenoid cystic carcinoma of the breast, cribriform carcinoma, Myofibroblastoma of the Breast (Benign spindle stromal tumor of the breast) and glycogen-rich clear cell carcinoma of the breast. There are numerous other rare breast cancers, including for example Fibromatosis of the breast (extra-abdominal desmoid), Angiomatosis of the Breast and mammary hamartoma. There are also nonmammary tumors, primarily adenocarcinomas, that can metastasize to the breast, including bronchogenic carcinomas, malignant melanomas (primary and secondary), rhabdomyosarcomas, malignant mesotheliomas, thyroid carcinomas, renal cell carcinomas, malignant lymphomas and gastrointestinal carcinomas (including those from the stomach, pancreas, esophagus and colon).

Colon cancers include many types which are rather diverse. Most are adenocarcinomas, either of the mucinous (colloid) type or the signet ring type. Less common colon cancers include squamous cell, neuroendocrine carcinomas, carcinomas of the scirrhous type, lymphomas, melanomas (i.e., primary or metastatic), sarcomas (e.g., fibrosarcomas and Leiomyosarcomas) and Carcinoid tumors.

Cancers of the prostate include adenocarcinomas, but others include small cell carcinoma, mucinous carcinoma, prostatic ductal carcinoma, squamous cell carcinoma of the prostate, basal cell carcinoma, neuro-endocrine carcinoma, signet-ring cell carcinomas and others.

Leukemia includes 4 different types of blood cancers: Acute Myelogenous, Acute Lymphocytic, Chronic Myelogenous and Chronic Lymphocytic Leukemias. The ways individuals with leukemia are affected and treated, the rate at which the disease progresses, are different for each leukemia type.

Lymphoma is a general term for a cancer group originating in the lymphatic system and divided into two major categories: Hodgkin lymphoma and all other lymphomas, called non-Hodgkin lymphomas.

The specification fails to identify the results of treatment with the methods of this invention and how such results would be recognized, particularly with regard to conditions and diseases that are currently considered fatal.

2. **Nature of the invention and predictability in the art:** The invention is directed toward medicine and is physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors

involved," and physiological activity is generally considered an unpredictable factor. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present:

> The first paragraph of 35 U.S.C. §112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

Plant Genetic Systems v. DeKalb Genetics, 65 USPQ2d 1452 (CAFC 2003).

3. **Direction and Guidance:** That provided is very limited. The dosage range information is meager at best. It is generic, the same for all disorders the specification covers. No specific direction or guidance provides a regimen or dosage effective specifically for all of the conditions construed by the claims.
4. **State of the prior art:** The art indicates the need for undue experimentation.

In regard to treatment of cancer, a review of the current literature substantiates the inability of researchers to locate a single therapy treatment for all types of cancers as is here claimed. Walsh, BBC News, International Version, Medical Notes, Feb. 1, 2007, quotes Prof. Fiona Watt, "We've known for many years that not all tumour cells are the same."

PharmaLicensing (Mar. 2005), reviewing a number of commercially available cancer treatments, reports:

> Effective cancer therapies are focused on the development of agents capable of selectively destroying tumour cells while sparing normal tissues. With this aim, major efforts have been directed at harnessing the specificity of the immune response. The discovery of hydridoma technology in the 1970s enabled the development of tumour-selective

> monoclonal antibodies (MAbs), creating a targeted therapeutic approach resulting in the selective death of cancer cells. … Despite the success of currently marketed cancer MAb therapies, however, the dream of a 'magic bullet' of antibody therapy has remained elusive.

Regarding NGFI-B, Barish, et al., Molecular Endocrinology 19 (10): 2466-2477, 2005, disappointingly report the low level of understanding:

> … 13 of 25 members of the orphan nuclear receptor family are expressed in macrophages. These include both constitutive activators [neuronal growth factor 1B (NGFIB), neuron-derived orphan A receptor (NOR) 1, nuclear receptor-related (NURR) 1, estrogen-related receptor (ERR) 1, RAR-related orphan receptor (ROR) α/γ, and germ cell nuclear factor] and constitutive repressors [chicken ovalbumin upstream promoter-transcription factor (COUP-TF) 3, orphan receptor encoded on the noncoding strand of the thyroid receptor-α and -ß, small heterodimeric partner, TR2, and TR4] that bind DNA either as monomers, homodimers, or RXR heterodimers. Despite such significant representation, their functions within the macrophage are virtually unknown.

Ramsden, et al., J. Clin. Pathol: Mol. Pathol. 2001; 54:369-380, call into question any effective relationship between NGFI-B and such diseases/disorders as Parkinson's Disease, cancer, Alzheimer's disease and schizophrenia, suggesting the need for additional research where a correlation between NGFI-B and any of these diseases/disorders are concerned. Regarding PD:

> Of possible relevance to idiopathic Parkinson's disease are the facts that: (1) both NGFI-B and NOR-1 are expressed in the caudate/putamen, the target site for dopaminergic neurons from the substantia nigra, but are not expressed in the substantia nigra itself; and (2) NGFI-B, NOR-1, and Nurr 1 are involved in the regulation of dopamineric neurone formation in the olfactory bulb, where NGFI-B is strongly expressed in the glomerular and granule cell layers."

Regarding cancer:

> After exposure of the prostate cancer cell line LNCaP to 6-[3-(1-adamantyl)-4-hydroxyphenyl]-3-chloro-2-naphthalene carboxylic acid and other proapoptotic agents, human NGFI-B was induced and the protein

was shown to move from the nucleus to the mitochondrion to trigger cytochrome c release. Therefore, in its role in apoptosis, human NGFI-B is not required to initiate gene transcription. Signals directing movement out of the nucleus were contained in both the N-terminus and C-terminus of the molecule. Apoptosis was inhibited by antisense human NGFI-B mRNA. In contrast, epidermal growth factor (EGF) - a non-apoptotic stimulus – also induced human NGFI-B mRNA, but the protein produced stayed within the nucleus and was capable of initiating gene transcription. Therefore, it seems that the contrasting actions of human NGFI-B are modulated by its intracellular localization, which in turn is dependent upon the natured or the signal to which the cell is exposed.

Regarding AD:

Both NGFI-B and NOR-1 generally are regarded as proapoptotic factors in tissue outside the CNS. This appears to be true for NGFI-B in the adult human CNS, too, with high amounts of the receptor being detectable in the brains of patients with Alzheimer's disease. However … both NGFI-B and NOR-1 are constitutively expressed in some regions of the brain in adult life where high rates of apoptotic neural death are not occurring, so obviously they have other functions, and in a model system where overexpression of NGFI-B was induced, it inhibited ceramide induced apoptosis but not the Fas-Fas ligand pathway."

Regarding a relationship between NGFI-B and transplant success, Tao, Hapatobiliary Pancreat. Dis. Int., Vol. 6, No. 4, Aug. 15, 2007, pages 348-357, noted (p. 351) the need for further research:

[A]lthough T cells normally express Nur77 [also called NGFI-B] after activation, we found that over-expression of Nur77 in allo-activated T cells might be a novel way to achieve transplant tolerance. Mimicking its proapoptotic role in thymocyte development, Nur77 over-expression caused a dramatic reduction of peripheral mature T cell population. More importantly, these T cells underwent increased apoptosis upon activation in vitro and in vivo, suggesting that Nur 77 is also an important regulator of mature T cell apoptosis. Interestingly, CD4+CD25+ naturally-occurring Tregs seemed to be more resistant to apoptosis by Nur77 over-expression, thus the 2nd lymphoid organs in Nur77Tg mice contain a large fraction of CD4+Foxp3+ T cells in comparison to wild type (WT) mice. Since Nur77 forms a complex with Foxp3 and HDAC7, whether Foxp3 or

certain HDAC(s) plays a protective role in Nur77 induced apoptosis warrants future studies.

Regarding any relationship between NGFI-B and schizophrenia or bipolar (manic depressive) disorder, Xing, et al., Schizophrenia Research, Vol. 84, No. 1, May 2006, Pages 36-56, report the need for further research:

> The potential effects of chronic antipsychotics on cortical NGFI-B and Nurr1 expression in patients with schizophrenia and bipolar disorders deserve further consideration. Although no significant correlations between the life-time dose of antipsychotics and Nurr1 and NGFI-B mRNA and protein expression were found in this study, chronic antipsychotics appear to have differential effects on NGFI-B mRNA expression in different brain regions of rats. Haloperidol treatment significantly increased NGFI-B mRNA in rat striatum and accumbens core, but abolished NGFI-B mRNA expression in primary somatosensory cortex. However, chronic clozapine treatment … resulted in a significant reduction in NGFI-B mRNA in nucleus accumbens, putamen, and medial prefrontal cortex and abolished NGFI-B mRNA expression in primary somatosensory cortex of the rat. Thus, it remains to be further clarified whether antipsychotic treatment could have contributed to the observed decreases in NGFI-B mRNA in schizophrenia.

Regarding any relationship between NGFI-B and inflammation, such as neuronal inflammatory response and acute inflammatory reactions, Martens, et al., Molecular Endocrinology 19 (4): 885-897, 2005, reported research that requires further study:

> The repressor activity of GR is an essential feature of its antiinflammatory activity. It was shown that GR exerts its repressor activity through antagonism of positively acting transcription factors such as NFκB and AP-1. We have shown recently that GR antagonizes transcription elicited by immediate early response genes of the nuclear receptor family. Indeed, **transcription elicited by NGFI-B (Nur77) is antagonized by GR.** The mechanism of this antagonism appears to be quite similar to transrepression observed between GR and NFκB or AP-1. In the present work, we have further defined the mechanism of transrepression between GR and the orphan nuclear receptors related to NGFI-B (Nur77) by

showing that the two other related orphan nuclear receptors, Nurr1 and NOR-1, are also targets of GR antagonism.

Regarding any relationship between NGFI-B and stroke, Dahlqvist, et al., Neuroscience, 2003;119(3):643-52, reported social interaction as a major component contributing to murine stroke recovery:

> Housing rats in an enriched environment improves functional outcome after ischemic stroke, this may reflect neuronal plasticity in brain regions outside the lesion. Which components of the enriched environment that are of greatest importance for recovery after brain ischemia is uncertain. We have previously found that enriched environment and social interaction alone both improve functional recovery after focal cerebral ischemia, compared with isolated housing with voluntary wheel-running. In this study, the aim was to separate components of the enriched environment and investigate the effects on some potential mediators of improved functional recovery; such as the inducible transcription factors nerve growth factor-induced gene A (NGFI-A) and NGFI-B, and the glucocorticoid and serotonin systems. After permanent middle cerebral artery occlusion, rats were divided into four groups … mRNA expression of inducible transcription factors, serotonin and glucocorticoid receptors was determined with in situ hybridisation 1 month after cerebral ischemia. Rats housed in enriched or social environments showed significantly higher mRNA expression of NGFI-A and NGFI-B in cortical regions outside the lesion and in the CA1 (cornu ammonis region of the hippocampus), compared with isolated rats with or without a running wheel. NGFI-A and NGFI-B mRNA expression in cortex and in CA1 was significantly correlated to functional outcome. … In conclusion, we have found that social interaction is a major component of the enriched environment regarding the effects on NGFI-A and NGFI-B expression.

Concerning a relationship between NGFI-B and arthritis or atherosclerosis, Lammi, et al., Mol. Endocrinol, Jun 2004, 18(6):1546-1557, proposes an area for future research:

> Nurr1 and the related orphan receptors NGFI-B and Nor1 Have been suggested to have roles in inflammatory processes such as rheumatoid arthritis and glomerulonephritis, in atherosclerotic lesions, in development

of extraskeletal myxoid chondrosarcoma, and in regulation of cell proliferation.

Ability of an agent that exhibits the specific activities shown in the specification to treat all diseases recited by the claims remains open to further study and proof.

5. **Working Examples:** Applicants do not provide highly predictive competent evidence or recognized tests to treat all conditions recited for the claims. Furthermore, Applicants have not provided competent evidence that the instantly disclosed tests are highly predictive for all uses disclosed and embraced by the claim language for all of the intended hosts.
6. **Skill of those in the art:** Walsh, Watt, PharmaLicensing, Barish, Ramsden, Tao, Xing, Martens, Dahlqvist and Lammi call into question the ability of a single class of compounds to effectively prevent and treat, not only all types of cancers, but all of the other diseases construed by the claims. These references discussed above confirm the need for additional research.
7. **Quantity of experimentation needed to make or use the invention.** Based on the disclosure's content, an undue burden would be placed on one skilled in the pharmaceutical arts to use the invention, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use, for reasons explained above. The state of the art, as discussed in the articles referenced above, indicates the requirement for undue experimentation. Thus, the ability of an agent that exhibits the specific activities shown in the specification to treat all of the diseases construed by the present claims remains open to further study and proof.

See MPEP 2164.01(a), discussed *supra*, justifying the conclusion of lack of enablement commensurate with the claims. Undue experimentation will be required to practice Applicants' invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14, 34 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. "FIG. 1" "for example"

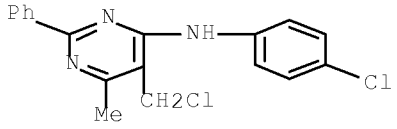
Rejections Under 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

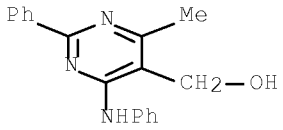
Claims 1-14 are rejected under 35 USC 102(a) over Cieplik, et al., Acta Poloniae Pharmaceutica (2003), 60(6), 487-492, Describing compositions of RN 164926-93-6, 4-

Pyrimidinamine, 5-(chloromethyl)-N-(4-chlorophenyl)-6-methyl-2-phenyl-,



, showing antibacterial and antifungal activity.

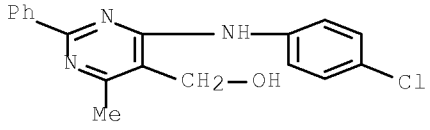
Claims 1-14 are rejected under 35 USC 102(a) over Cieplik, et al., Bollettino Chimico Farmaceutico (2003), 142(4), 146-150, describing compositions of RN 154957-59-2, 5-Pyrimidinemethanol, 4-methyl-2-phenyl-6-(phenylamino)-,



, having antibacterial activity.

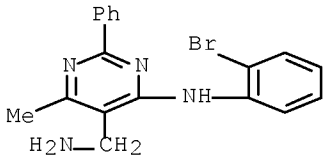
Claims 1-14 are rejected under 35 USC 102(a) over Cai, et al., US 7226927, entitled to the date of Dec. 12, 2000, describing compositions as inducers of apoptosis comprising 2-aryl-4-aryylaminopyrimidines (see col. 6, lines 25-54, *inter alia*); also see the compounds/compositions exemplified throughout the specification.

Claims 1-14 are rejected under 35 USC 102(b) over Cieplik, et al., PL 194083, published 20070430, describing compositions of RN 154957-61-6, 5-Pyrimidinemethanol, 4-[(4-chlorophenyl)amino]-6-methyl-2-phenyl-,



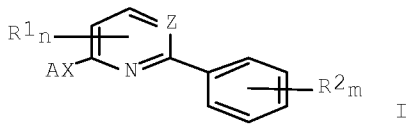
, with immunotropic activity.

Claims 1-14 are rejected under 35 USC 102(b) over Cieplik, et al., Scientia Pharmaceutica (2002), 70(3), 245-252, describing compositions of RN 515167-37-0, 5-Pyrimidinemethanamine, 4-[(2-bromophenyl)amino]-6-methyl-2-phenyl-,



, having antibacterial properties.

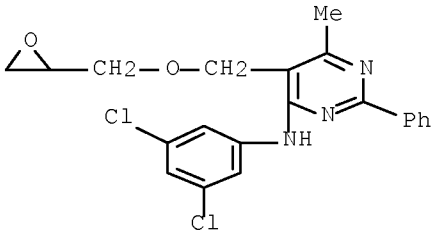
Claims 1-14 are rejected under 35 USC 102(b) over Kleeman, et al., US 5849758, issued 19981215, describing herbicidal compositions of 2,4-disubstituted pyrimidines,



I , in which Z = N; A = substituted aryl or (un)substituted pyridyl or pyrazolyl; n = 0, 1 or 2; R1 = H or (un)substituted alkyl, alkoxy, alkylthio or dialkylamino; m = 0, 1-5; R2 = H, halo, (un)substituted alkyl, haloalkyl, haloalkoxy, alkoxy, alkylthio, or nitro, cyano or halosulfonyl; and X = O or S. See the specific compounds exemplified at col. 3, line 66; at col. 4, lines 7, 9, 42, 44, 50, 54, 58, 64, 66; at col. 5, lines 12, 24, 26, 39, 46, *inter alia*.

Claims 1-14 are rejected under 35 USC 102(b) over Cieplik, et al., Archiv der Pharmazie (Weinheim, Germany) (1997), 330(8), 237-241, describing antibacterial

compositions of RN 198978-67-5, 4-Pyrimidinamine, N-(3,5-dichlorophenyl)-6-methyl-5-[(oxiranylmethoxy)methyl]-2-phenyl-,



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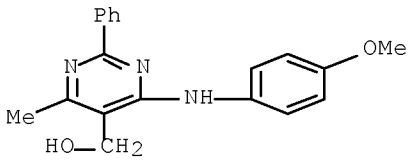
Claims 1-14 are rejected under 35 USC 102(b) over Cieplik, et al., Bollettino Chimico Farmaceutico (1996), 135(8), 459-464, describing antibacterial compositions of RN 186804-30-8, 5-Pyrimidinemethanol, 4-[(4-methoxyphenyl)amino]-6-methyl-2-phenyl-,



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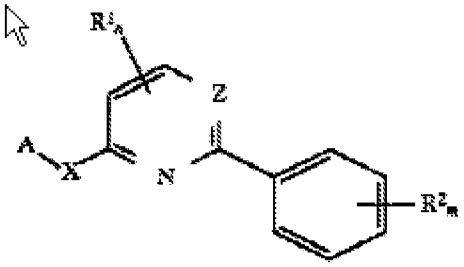
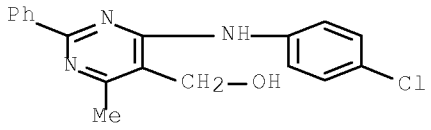
Claims 1-14 are rejected under 35 USC 102(b) over Kleemann, et al., US 5824624, issued 19981020, describing herbicidal compositions of 2,4-disubstituted pyrimidines



(I)

, in which A = optionally substituted aryl or optionally substituted 5- or 6-membered N-containing heteroarom group; m = 0-5; n = 0-2; R1 (or each R1) = H, halo, optionally substituted alkyl, alkenyl, alkynyl, alkoxy, (di)alkoxyalkyl, alkoxyalkoxy, alkylthio, (di)(alkyl)amino, alkoxyamino, formamidino; R2 (or each R2) = H, halo, optionally substituted alk(en/yn)yl, alkoxy, alkylthio, alkylsulfonyl, alkylsulfinyl, NO2, cyano, haloalkyl, haloalkoxy, haloalkylthio; X = O or S; Z = N. See the specific compounds exemplified at col. 3, lines 7, 14, 16, 48, 50, 56, 60, 64; at col. 4, lines 3, 5, and Examples 22, 30, 76, 91, 95, 97, *inter alia*.

Claims 1-14 are rejected under 35 USC 102(b) over Machon, et al., PL 164076, published 19940630, describing immunostimulant compositions of 2-phenyl-4-(4'-chlorophenylamino)-6-methyl-5-(hydroxymethyl)pyrimidine,



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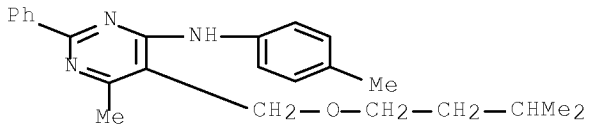
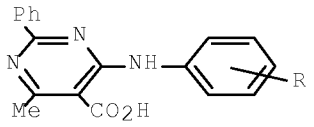
Claims 1-14 are rejected under 35 USC 102(b) over Cieplik, et al., Farmaco (1995), 50(2), 131-6, Describing immunomodulatory compositions of RN 164927-13-3, 4-Pyrimidinamine, 6-methyl-5-[(3-methylbutoxy)methyl]-N-(4-methylphenyl)-2-phenyl-,



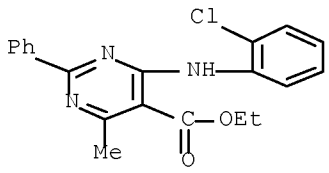
.

Claims 1-14 are rejected under 35 USC 102(b) over Cieplik, et al., Acta Poloniae Pharmaceutica (1994), 51(1), 59-62, Describing antibacterial compositions of



I , in which R = 2-Cl, 4-Cl, 3,4-Cl2, 3,5-Cl2, 4-OH, 4-Me, and 4-Cl, 3-F (II), as well for their Et esters;

Exemplified by RN 94036-93-8, 5-Pyrimidinecarboxylic acid, 4-[(2-chlorophenyl)amino]-6-methyl-2-phenyl-, ethyl ester,



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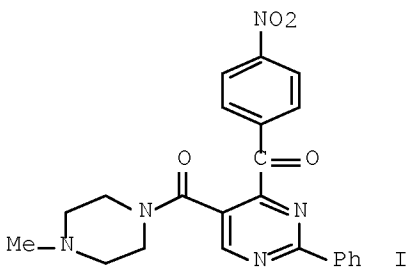
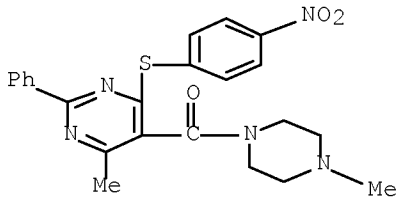
Claims 1-14 are rejected under 35 USC 102(b) over Ohkubo, et al., Chemical & Pharmaceutical Bulletin (1994), 42(6), 1279-85, describing cerebral protective compositions of 5-(4-methylpiperazin-1- ylcarbonyl)-4-(4-nitrobenzoyl)-2-phenylpyrimidine



I

, and

RN 116904-26-8, Piperazine, 1-methyl-4-[[6-methyl-4-[(4-nitrophenyl)thio]-2-phenyl-5-pyrimidinyl]carbonyl]-,



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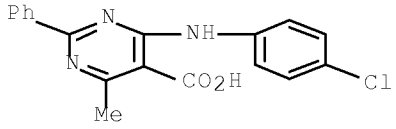
Claims 1-14 are rejected under 35 USC 102(b) over Machon, et al., PL 130888, published 19840929, describing pathogenic compositions of RN 94036-97-2, 5-Pyrimidinecarboxylic acid, 4-[(4-chlorophenyl)amino]-6-methyl-2-phenyl-,



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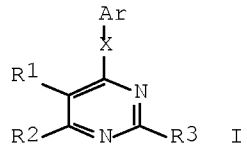
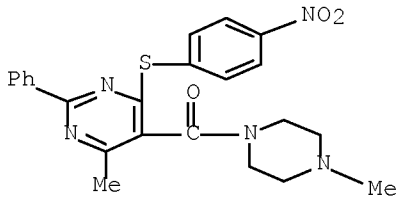
Claims 1-14 are rejected under 35 USC 102(b) over Takatani, et al., JP 63107966, published 19880512, describing compositions for treating disease and disorders of cerebral blood vessels of



I , in which Ar = (nitro or habalkyl)aryl, fused benzene-heterocyclyl containing N or O; X = bond, lower hydroxyalkylene, lower alkenylene, NH, S, CO; R1 = (esterified) CO2H, lower hydroxyalkyl, lower haloalkyl, (N-substituted) CONH2 or lower aminoalkyl; R2 = H, lower alkyl; optionally R1R2 completing (substituted) N-containing heterocycle; R3 = aryl;

Exemplified by RN 116904-26-8, Piperazine, 1-methyl-4-[[6-methyl-4-[(4-nitrophenyl)thio]-2-phenyl-5-pyrimidinyl]carbonyl]-,



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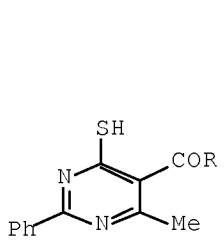
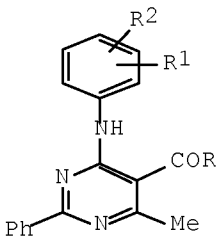
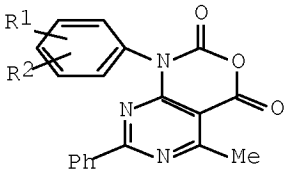
Claims 1-14 are rejected under 35 USC 102(b) over Machon, et al., European Journal of Medicinal Chemistry (1984), 19(4), 359-63, describing antibacterial compositions of



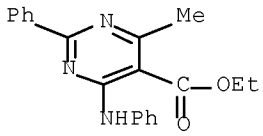
I 

II 

III , wherein in Formula I, R = OEt, OH, and wherein in Formula II R = OH, NHEt, NEt2, NHC6H4OEt-

4, NHC6H4Cl-4; R1 = H, 4-Cl; R2 = H, 4-OEt, 4-Cl, Cl, 3-Cl, 2-Cl, 3-CF3;

Exemplified by RN 94037-15-7, 5-Pyrimidinecarboxylic acid, 4-methyl-2-phenyl-6-(phenylamino)-, ethyl ester,



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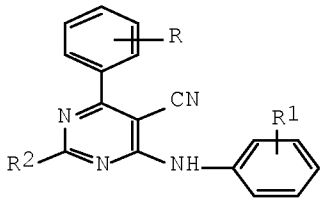
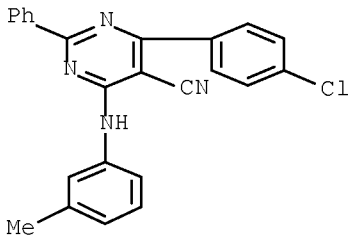
Claims 1-14 are rejected under 35 USC 102(b) over Mincheva, Doklady Bolgarskoi Akademii Nauk (1980), 33(7), 925-7, Describing bactericidal compositions of



I

, in which R = 2-Cl, 3-Cl, 4-Cl; R1 = H, 3-Me, 2-OMe; R2 = Ph, 2-naphthyl, 4-Me2NC6H4;

Exemplified by RN 76851-25-7, 5-Pyrimidinecarbonitrile, 4-(4-chlorophenyl)-6-[(3-methylphenyl)amino]-2-phenyl-,



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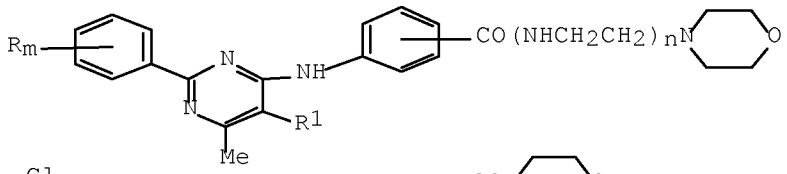
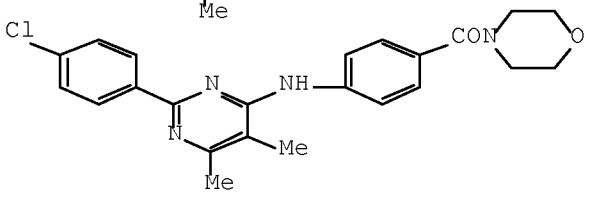
Claims 1-14 are rejected under 35 USC 102(b) over Fauran, et al., US 4041030,

issued 19770809, describing antianoxic compositions, *inter alia*, comprising



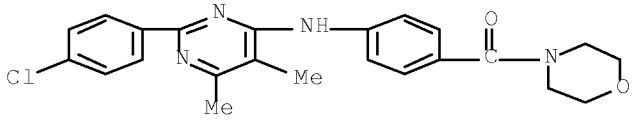
I



II

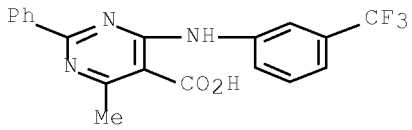
, wherein in Formula I, R = H, halo, C1-3 alkoxy; R1 = H, Me; n = 0, 1; m = 0-3;

Exemplified by RN 65789-84-6, Morpholine, 4-[4-[[2-(4-chlorophenyl)-5,6-dimethyl-4-pyrimidinyl]amino]benzoyl]-,



, and the compounds in the Tables.

Claims 1-14 are rejected under 35 USC 102(b) over Kim, et al., US 3860596, issued 19750114, describing CNS depressant and anti-inflammatory compositions comprising 2-aryul-4-substituted-amino-5-pyrimidyl compounds (col. 1, lines 26-67, *inter alia*,) exemplified by RN 55914-58-4, 5-Pyrimidinecarboxylic acid, 4-methyl-2-phenyl-6-[[3- (trifluoromethyl)phenyl]amino]-,



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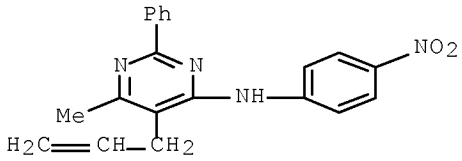
Claims 1-14 are rejected under 35 USC 102(e) over Nieland, et al., WO 2004032716, entitled to the date of 20031008, describing compositions of RN 330819-79-9, 4-Pyrimidinamine, 6-methyl-N-(4-nitrophenyl)-2-phenyl-5-(2-propen-1-yl)-,



for regulation of lipid and cholesterol uptake.

Objectionable Claims

Claims 1-36 are objectionable as directed to elected and non-elected subject matter. They should be amended to recite elected subject matter, as set forth above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cecilia M. Jaisle, J.D. whose telephone number is 571-272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Cecilia M. Jaisle, J.D.

5/5/2008

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624